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Optimizing the Clinical Use of Vancomycin

Rocío Álvarez, Luis E. López Cortés, José Molina, José M. Cisneros, Jerónimo Pachón

Clinical Unit of Infectious Diseases, Microbiology, and Preventive Medicine, Instituto de Biomedicina de Sevilla (IBiS), Hospital Universitario Virgen del Rocío-Hospital Universitario Virgen Macarena/CSIC/Universidad de Sevilla, Seville, Spain

The increasing number of infections produced by beta-lactam–resistant Gram-positive bacteria and the morbidity secondary to these infections make it necessary to optimize the use of vancomycin. In 2009, the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, and the Society of Infectious Disease Pharmacists published specific guidelines about vancomycin dosage and monitoring. However, these guidelines have not been updated in the past 6 years. This review analyzes the new available information about vancomycin published in recent years regarding pharmacokinetics and pharmacodynamics, serum concentration monitoring, and optimal vancomycin dosing in special situations (obese people, burn patients, renal replacement therapy, among others). Vancomycin efficacy is linked to a correct dosage which should aim to reach an area under the curve (AUC)/MIC ratio of ≥400; serum trough levels of 15 to 20 mg/liter are considered a surrogate marker of an AUC/MIC ratio of ≥400 for a MIC of ≤1 mg/liter. For *Staphylococcus aureus* strains presenting with a MIC >1 mg/liter, an alternative agent should be considered. Vancomycin doses must be adjusted according to body weight and the plasma trough levels of the drug. Nephrotoxicity has been associated with target vancomycin trough levels above 15 mg/liter. Continuous infusion is an option, especially for patients at high risk of renal impairment or unstable vancomycin clearance. In such cases, vancomycin plasma steady-state level and creatinine monitoring are strongly indicated.

Vancomycin has traditionally been used as a first-line agent for treating methicillin-resistant *Staphylococcus aureus* (MRSA) and other Gram-positive beta-lactam–resistant bacteria (1), which are frequent etiologies of severe health-related infections (2, 3).

Although the effectiveness of vancomycin is supported by more than 5 decades of use and multiple studies, the clinical and microbiological scenario in which it is used is always changing. Attaining an appropriate dosage of vancomycin for *S. aureus* infections might be difficult due to the clinical impact of the creep in the MIC of vancomycin and heteroresistance among MRSA strains, or due to complex pharmacokinetic and pharmacodynamic (PK/PD) situations. In this context, the American Society of Health-System Pharmacists (ASHP), the Infectious Diseases Society of America (IDSA), and the Society of Infectious Diseases Pharmacists (SIDP) introduced a practice guideline in 2009 (4), marking a milestone in vancomycin therapy. However, several questions, such as the optimal dosing in some special clinical situations (e.g., with renal replacement therapies or in burn patients or obese patients), the role of continuous infusion, or the renal toxicity when the suggested vancomycin serum levels are achieved, remain unanswered. The present review mainly focuses on these issues.

VANCOMYCIN PHARMACODYNAMICS AND ITS IMPLICATIONS FOR DRUG MONITORING

The killing effect of vancomycin is characterized by a slow mode of action and is further hampered by a large bacterial inoculum, a stationary growth phase, and anaerobic conditions (5, 6). Although several pharmacodynamic parameters have been proposed to determine vancomycin activity, data from experimental and clinical studies have selected the area under the curve (AUC)/MIC ratio as the best parameter to predict the effectiveness of vancomycin (4, 7–9). The target consensus of an AUC/MIC ratio of ≥ 400 for MRSA infections is supported by *in vitro* data, animal models, and clinical studies that have related an AUC/MIC ratio of 350 to 400 to successful outcome (7–18). However, it must be noted that the vancomycin MIC for *S. aureus* varies depending on the testing method used. Etest yields MICs of 0.5- to 1.5-$\log_2$ dilutions higher than those determined by broth microdilution (BMD) (10, 14–19). In this review, unless otherwise noted, all of the AUC/MIC ratios are Etest measures; Etest is the recommended method for measuring the MIC for MRSA bloodstream infection isolates (18).

Using an experimental murine model of MRSA pneumonia, our group found that an optimized dose of vancomycin (AUC/MIC ratio ≥ 400) was more efficacious than lower doses of vancomycin in the clearance of bacteria from lungs and blood, even though it could not demonstrate a higher survival rate (20). In clinical studies, an AUC/MIC ratio around 400 is related to the best survival rate or to clinical success in patients with *S. aureus* bacteremia, although other thresholds have been observed (10, 17, 18, 21). In a cohort of 182 patients with *S. aureus* bacteremia, an AUC/MIC ratio of >373 was identified as the breakpoint significantly associated with lower 30-day mortality (odds ratio [OR], 0.44) using the BMD method. Zelenitsky et al. (21) found that, in a group of 35 patients with MRSA-associated septic shock, the survival rate was greater in those with higher AUC/MIC values, reaching 70% when the AUC/MIC ratio was ≥451 ($P = 0.006$) and 81.8% when the AUC/MIC ratio was ≥578 ($P = 0.012$). Nonetheless, these results should be interpreted with caution: the AUC was constructed with a population PK model using just one serum level determination, and a MIC of 1 mg/liter was assumed

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Address correspondence to Jerónimo Pachón, pachon@us.es.

based on surveillance BMD data. A recent retrospective cohort study (18), which used Bayesian methods to estimate the vancomycin exposure profile in 123 patients with MRSA bacteremia, showed that failure (defined as 30-day mortality, bacteremia for ≥ 7 days, or recurrence) was less in those cases achieving an AUC/MIC_{Etest} ratio of ≥ 303 and ≥320 (relative risk [RR], 0.5) on day 1 and day 2, respectively or an AUC/MIC_{BMD} ratio of ≥ 521 (RR = 0.6) and ≥650 (RR = 0.5) on day 1 and day 2, respectively.

Peak vancomycin serum levels do not correlate to toxicity or efficacy (22). Instead, trough serum levels at steady-state conditions have been proposed as a more accurate and practical method to monitor vancomycin. Guidelines for vancomycin therapy are clear in stressing the importance of therapeutic drug monitoring and the use of the trough concentration as a surrogate for the target AUC. The main guidelines recommendations are to administer dosages of 15 to 20 mg/kg of body weight every 8 to 12 h to achieve target trough levels of 15 to 20 mg/liter and to start monitoring the vancomycin trough concentration before the fourth dose (4). This strategy is based in several premises. First, vancomycin efficacy and toxicity are both related to the AUC, with a quite narrow therapeutic ratio. Second, determining the AUC requires multiple serum vancomycin samples, and a different strategy is needed in the clinical setting to make monitoring easier. However, whether trough levels are an optimal surrogate of AUC is still a source of controversy. In the PK/PD study with a series of Montecarlo simulations performed by Patel et al. (23), a wide range of AUC values from several dosage regimens yielding isometric C_{min} values, and vice versa, was found. The simulations also showed that the likelihood of achieving an AUC/MIC ratio of >400 was virtually 100% with different dosage regimens when the trough was 15 to 20 mg/liter and the MIC was ≤1 mg/liter, but the likelihood gradually decreases with the MIC growth. Neely et al. (24) have published the largest population PK model, which is based on three previous data sets from 47 richly sampled adults receiving vancomycin. Their results bear out a noteworthy interpatient variability of AUC, trough, and peak values. These authors performed a two-compartmental model based on the full data set that fitted the observed concentrations well (R^2 = 0.902). They found that the AUCs estimated from the trough and the peak-trough data sets were lower than the AUCs from the full data sets, with a difference of 341.9 mg/liter ($P < 0.001$) and 159.3 mg/liter ($P <$ 0,001), respectively. Notwithstanding, up to 60% of adults who achieved a therapeutic AUC of >400 mg · h/liter would have had a trough concentration below 15 mg/liter (24). This stresses that, for strains with a MIC of ≤1 mg/liter, trough concentrations of 15 mg/liter might usually be enough to achieve the target AUC/MIC ratio of ≥400. Otherwise, if the vancomycin MIC is >1 mg/liter, an alternative agent should be considered. It must be stressed that this recommendation could not apply to *S. aureus* strains showing heteroresistance to vancomycin. Heterogeneous vancomycin-intermediate *S. aureus* (hVISA) strains exhibit a vancomycin MIC in the susceptible range but include up to $1/10^5$ to $1/10^6$ bacterial subpopulations with increased MIC (84). The real prevalence of hVISA is unknown; notwithstanding, current data indicates that it is growing. In addition, the proportion of hVISA increases as the vancomycin MIC are >1 mg/liter (85).

Due to this relevant interindividual variability correlating vancomycin trough levels with the AUC/MIC ratio, guiding vancomycin dosing exclusively based on trough levels may be insufficient. A more accurate approach has been provided by linear regression analysis, population PK models, and Bayesian estimation procedures (25).

Linear regression analysis estimates dosing based in two serum determinations, assuming a one-compartment model. It is an easy method but is not particularly accurate in a changing situation (e.g., renal function) (25).

Population methods use population PK parameters to design nomograms for calculating dosages, but these methods have several drawbacks. First, they assume a linear correlation between renal function and vancomycin clearance. Second, they usually seek to ensure target trough levels, not a target AUC. In addition, only a few nomograms have been developed to achieve the current target endpoints. The studies from Wesner et al. (26) and Kullar et al. (27) targeted different trough levels, and those from Revilla et al. (28) constructed nomograms to achieve an AUC/MIC ratio of ≥400. In all cases, application to populations of patients excluded from the studies should be avoided.

The third method, Bayesian estimation procedures, combines optimized population information with PK information from the patient for calculating doses. It is the most accurate procedure when correctly used. By Bayesian techniques, vancomycin dosages can be calculated to achieve a target AUC/MIC; therefore, they avoid the use of trough serum levels as a surrogate target (18). The main drawback is that Bayesian techniques require exact information about many parameters, such as age, weight, renal function, and previous therapeutic regimen, among others. Another disadvantage is the need for trained personnel with specialized pharmacokinetics knowledge (25).

LOADING DOSE

A loading dose of 25 to 30 mg/kg has been proposed as an appropriate strategy in order to avoid subtherapeutic vancomycin levels in the initial stages of therapy. This recommendation is based on one randomized clinical trial (RCT) (29) and on other studies evaluating trough serum vancomycin levels after a loading dose on different types of patients (Fig. 1) (30–32). The previously mentioned RCT (29) assayed a loading dose of 25 to 30 mg/kg in critically ill patients. Regrettably, it presented the caveat that the authors only determined peak vancomycin levels, despite peak levels not correlating to efficacy (29). Recently, Rossini et al. (30) performed an RCT on 99 patients receiving a loading dose of 30 mg/kg of vancomycin or the standard therapy with 15 mg/kg. After 12 h, the proportion of patients achieving a trough level of 15 mg/liter was higher in the group with loading dose (34% versus 3%; $P < 0.01$), without toxicity differences between them. This study included both critically and noncritically ill patients. Truong et al. (31) failed to find differences in the proportion of patients with trough vancomycin levels of ≥15 mg/liter in a pre- and postintervention study when comparing standard therapy with a fixed loading dose of 2 g in 52 critically ill patients. Despite that, the mean (± standard deviation [SD]) trough plasma concentrations were higher in the postintervention group (9.8 ± 6.6 versus 14.9 ± 6.3 mg/liter). However, the sample is lacking statistical power, with just 11 patients receiving the loading dose. Vandecasteele et al. (32) proposed a loading dose for patients undergoing hemodialysis. It was calculated according to dry body weight and the period to the next dialysis session. The usefulness of a loading dose to achieve the targeted trough levels early in other groups of patients has not been assessed. In summary, selected patients with severe disease may benefit from a vancomycin

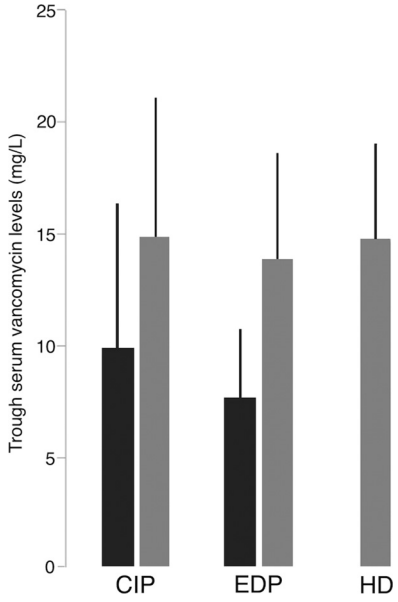

FIG 1 Recommendations of a vancomycin loading dose (LD), to achieve early therapeutic levels, have been established after several studies evaluating trough serum vancomycin concentrations after an LD. In critically ill patients (CIP), trough vancomycin levels (mean ± SD) after a fixed LD of 2 g (≈30 mg/kg, n = 21 patients) was higher than in patients without an LD (n = 31) (P = 0.01) in an intervention observational study (31) (evidence level IIB [83]). In patients presenting to an emergency department (EDP), trough levels (mean ± SD) after an LD of 30 mg/kg (n = 50) were higher than without an LD (n = 49) ($P < 0.001$) in a randomized clinical trial (30) (evidence level IA [83]). Finally, in patients on hemodialysis (HD) (n = 15), trough serum levels (mean ± SD) after an LD of 20 mg/kg (32) were similar to those found in the above-mentioned two studies carried out in patients with normal renal function (evidence level IIC [83]).

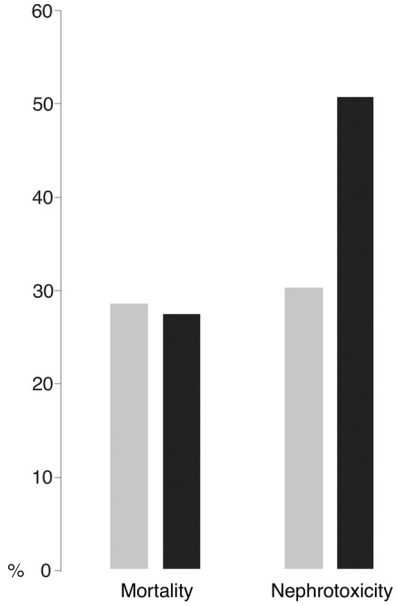

FIG 2 Continuous (CoI) versus intermittent (InI) vancomycin infusion impact on mortality and nephrotoxicity has been evaluated through a systematic review and meta-analysis of vancomycin for the treatment of Gram-positive infections (34). The global mortality was not different between patients on CoI versus those on InI (RR, 1.03; 95% CI, 0.7 to 1.6; P = 0.9). On the contrary, nephrotoxicity was higher in patients receiving vancomycin InI than in those with CoI (P = 0.02).

loading dose with the aim of achieving early steady-state levels. Further studies are needed to clarify the clinical impact of applying a loading dose in all kinds of patients.

INTERMITTENT VERSUS CONTINUOUS INFUSION THERAPY

All efforts to demonstrate differences in the effectiveness of continuous infusion (CoI) and intermittent infusion (InI) have failed (33–35). In contrast, there are many reports of a reduced toxicity of CoI with respect to InI (36). Cataldo et al. (34) performed a meta-analysis comparing these two dosing approaches and concluded that CoI achieved a similar overall mortality rate and less renal impairment (Fig. 2). Of note, only six studies, quite heterogeneous (I^2 of 90% for vancomycin exposure, I^2 of 0 for nephrotoxicity and mortality), could be included, and just one was a randomized clinical trial, so results cannot be considered conclusive. Subsequently, Hanrahan et al. (37) found a significant association between InI and nephrotoxicity in a retrospective cohort of 1,430 critically ill patients (OR, 8.2). Thus, the available information encourages using CoI when a high risk of nephrotoxicity exists, such as in the coadministration of other nephrotoxic agents (aminoglycosides or loop diuretics), in the presence of septic shock, or in patients needing high vancomycin doses (those with central nervous system infection or obese patients). Stronger evidence would be welcome.

In addition, CoI has other advantages, such as easier monitoring and lower price (33). It is an attractive option for the treatment and monitoring of outpatients, in which an efficacy similar to InI has been shown (35), and on busy nursing wards. Continuous vancomycin infusion might require less therapeutic drug monitoring, and samples can be obtained anytime after the first 18 to 24 h (38). This could be useful for patients with unstable vancomycin clearance (burns patients, patients under continuous renal replacement therapy). The solution of vancomycin for CoI should be stable for at least 72 h, although careful attention must be paid to incompatibilities with other medications in the same infusion (39).

Different target steady-state levels have been proposed. A PD study reasserted that bacterial killing and development of diminished vancomycin susceptibility during CoI therapy were dependent on the AUC/MIC ratio, with values of 480 being bactericidal and suppressing emerging resistance; this target would be achieved with CoI at a steady-state concentration of 20 mg/liter when vancomycin pathogen MICs are 1 mg/liter (40). Other authors have suggested that, given the tendency toward increasing vancomycin MICs in clinical isolates of *S. aureus* in some centers, a target concentration of 25 mg/liter may be more appropriate (41). However, in this case, careful monitoring must be carried out. Norton et al. (42) and Spapen et al. (43) refer to the fact that steady-state concentrations of ≥32 mg/liter and >30 mg/liter, respectively, which are close to 25 mg/liter, were related to higher risks of nephrotoxicity in patients receiving CoI of vancomycin (Fig. 3).

The largest PK study on CoI of vancomycin showed that dosages need to be individualized according to the actual body weight (ABW) and creatinine clearance (CrCl) of the patient (44). To achieve a steady-state concentration of ≥20 mg/liter, these authors propose a minimum loading dose of 35 mg/kg, followed by

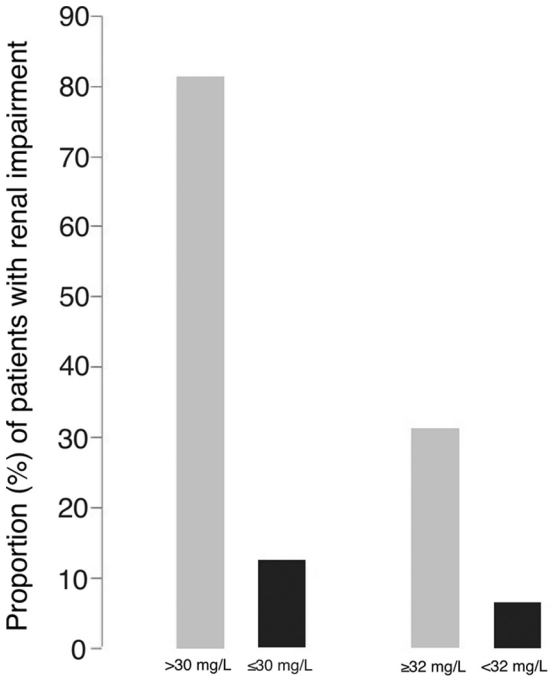

FIG 3 The suggested steady-state concentrations to be reached in vancomycin continuous infusion (CoI) should be between 20 and 30 mg/liter (evidence level IIB [83]), to avoid nephrotoxicity. Spapen et al. (43), in a retrospective cohort study carried out in critically ill patients, found high acute kidney injury frequency in patients with vancomycin levels of >30 mg/liter ($P < 0.01$). Norton et al. (42), in a retrospective outpatient cohort, found high nephrotoxicity in patients with vancomycin levels of ≥32 mg/liter ($P < 0.01$). The diverse types of patients and the nonhomogeneous criteria to determine nephrotoxicity may explain the difference in the proportions of nephrotoxicity between the two studies.

a daily dose adjusted to CrCl, based on a population PK analysis of retrospective data from critically ill patients. However, the efficacy and safety of this scheme have not been prospectively validated in clinical studies. Several administration protocols and nomograms validated in a few patient cohorts are available. They used different loading doses and also used diverse daily doses, for which calculations were based on estimates of CrCl by the Cockcroft-Gault formula, in order to achieve target steady-state concentrations of 15 or 20 mg/liter (45), 25 mg/liter (46), and 27.5 mg/liter (47). All of these schemes were developed in critically ill patient samples, so implementation in other patients may require closer monitoring.

RENAL REPLACEMENT THERAPIES

Many critically ill patients with sepsis need both vancomycin and a continuous renal replacement therapy (CRRT). A proper vancomycin dosage is crucial in order to achieve therapeutic levels without worsening renal function. However, some PK factors must be taken into consideration. Volume of distribution (V) may change rapidly in patients on continuous venovenous hemofiltration, and it is also related to the serum albumin, which can be unstable as well (48). The type of technique (hemofiltration, hemodialysis, or hemodiafiltration), the filter used, the effluent flow rate, the blood flow rate, and the pre- or postfilter volume reposition are the main factors influencing the PK of vancomycin in patients receiving CRRT (49). According to the regression analysis of published PK data performed by Jamal et al. (50), effluent flow rate seems to be the most reliable predictor of extracorporeal vancomycin clearance in patients with CRRT.

Different dosages, either for continuous or intermittent vancomycin therapy, have been proposed in recent PK observational studies (51–56) to understand the best dosages in patients receiving CRRT. CoI seems to be more successful under these conditions to achieve the PK/PD targets. The weight-based CoI proposed by Beumier et al. (52) achieved an AUC/MIC ratio of >400 in all patients with a MIC of ≤1 mg/liter and for 72% of patients when the MIC was 1.5 mg/liter. In contrast, the largest vancomycin population PK analysis conducted in patients undergoing CRRT and receiving CoI of vancomycin was not able to quantify the effect of CRRT on vancomycin pharmacokinetics (54). Escobar et al. (55) propose continuous infusion as the most useful alternative to maintain stable vancomycin levels during high-volume hemofiltration (HVHF). They performed a population PK study and estimated that, after a loading dose of at least 20 mg/kg, maintaining daily doses between 1 and 2 g/24 h (depending on the HVHF intensity) was required to achieve steady-state levels of vancomycin between 20 and 30 mg/liter. Probably, until prospective, multicenter studies provide robust information, weight-based loading dose, CoI, and frequent monitoring of vancomycin levels are best practices in patients on CRRT.

Vancomycin is very useful in patients undergoing intermittent hemodialysis, since it allows outpatients to be treated with intravenous therapy. Nonetheless, classic therapeutic schemes of fixed doses rarely achieve the target trough of 15 to 20 mg/liter. Lin et al. (57) described that an individualized loading dose of 15 to 20 mg/kg followed by a maintaining dose of 500 mg after each hemodialysis session provided trough serum concentrations of 10 to 20 mg/liter in 87% of patients. With a similar loading dose, Rymarz et al. (58) found that 72.7% of patients reached these concentrations. Nonetheless, in the reports by Lin et al. and Rymarz et al., just 68.1% and 27.2% of patients, respectively, achieved trough levels between 15 and 20 mg/liter. In the study by Vandecasteele et al. (32), fixed loading doses achieved vancomycin levels below 15 mg/liter in 87.2% of patients undergoing intermittent hemodialysis. These authors identified predialysis vancomycin trough levels, dry body weight, and time period to the next dialysis session as the parameters best related to vancomycin trough levels in these patients, and they subsequently developed a vancomycin dose calculator and validated it prospectively in an 18-patient cohort; in the cohort, up to 77.9% of patients achieved appropriate therapeutic levels of vancomycin. In a report by Jeremiah et al. (59), calculating the maintaining dose with a nomogram based only on the current trough levels, just 54.5% of patients obtained 15- to 20-mg/liter trough concentrations. Although the dosing of vancomycin in patients undergoing intermittent hemodialysis, to achieve early trough levels between 15 and 20 mg/liter, should generally include a loading dose of ≈20 mg/kg (Fig. 4), the above-cited studies point out that vancomycin therapy for patients undergoing intermittent dialysis must be individualized, taking into consideration as many relevant variables as possible. Moreover, to our knowledge, there is no data to confirm that trough levels of 15 to 20 mg/liter are surrogate markers of fixed AUC in patients on hemodialysis.

VANCOMYCIN AND OBESITY

There is a lack of available data about the dosing of antimicrobials in obese patients, and, focusing on vancomycin, these patients

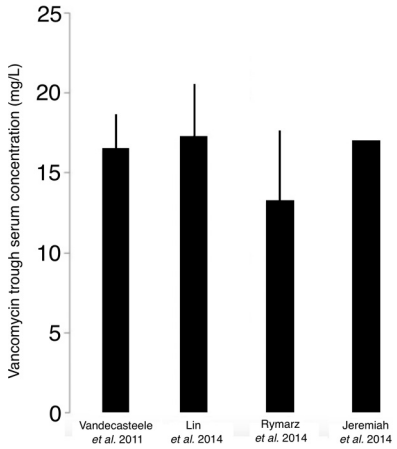

FIG 4 The dosing vancomycin in patients undergoing intermittent hemodialysis, to achieve vancomycin trough concentrations between 15 and 20 mg/liter, must include a loading dosage of ≈20 mg/kg (evidence level IIB [83]), as suggested by a study carried out to develop a vancomycin dose calculator (Vandecasteele et al. [32]) and by several observational studies (Lin et al. [57], Rymarz et al. [58], and Jeremiah et al. [59]) (data expressed as mean ± SD). Thereafter, using pharmacokinetics data from 41 patients (32), the estimated doses for different intervals to the next hemodialysis may be 15, 25, and 35 mg/kg for 1-day, 2-day, and 3-day elapse times, respectively.

frequently receive insufficient dosages (60). Obesity produces an increased volume of distribution for most antibiotics and different hepatic metabolism and renal excretion. Besides, it is associated with an increase in certain circulating proteins, which results in altered free serum vancomycin concentrations. Increased blood flow secondary to increased cardiac output and blood volume also occurs, resulting in increased vancomycin clearance (61). Achieving adequate vancomycin serum levels and similar efficacy without a high risk of toxicity is a current challenge (62). For obese patients, the most widespread recommendation is an initial dose based on ABW, not exceeding 2 g for each dose, and adjusting the subsequent doses based on serum vancomycin concentrations to achieve therapeutic levels (4). However, Reynolds et al. (63) found that these dosages are associated with a high risk of above-target trough levels. They compared the IDSA-based protocol with a revised one in 74 and 64 obese patients, respectively, reporting that the revised protocol better enabled them to reach trough concentrations of 10 to 20 mg/liter (36% versus 59% in IDSA-based versus revised protocol; $P = 0.006$). Nonetheless, the higher risk of low concentrations, the absence of demonstrated impact on toxicity, and the low target levels chosen for the study limit its application. Wesner et al. (26) developed a nomogram based on the dry weight to calculate dosages in obese patients. However, the achievement of therapeutic levels was 39% in obese patients, and the study excluded patients with a weight of >120 kg. Therefore, there is not enough data currently to make a statement to guide vancomycin dosing in obese patients.

BURN PATIENTS AND VANCOMYCIN

Burn patients present a higher vancomycin total body clearance (64). This leads to a low likelihood of achieving therapeutic vancomycin levels (65). Moreover, vancomycin PK changes with time after the incident, which makes it even more difficult to give fixed patterns of dosing (49). Therefore, there are no data about weight-adjusted vancomycin dosing in burn patients. Close monitoring of vancomycin serum concentrations is recommended to ensure targets are met and maintained. In a recent retrospective cohort study, burn patients receiving continuous infusion of vancomycin more frequently had levels in the therapeutic range and were less likely to have serum trough levels of <10 μg/ml, without differ-

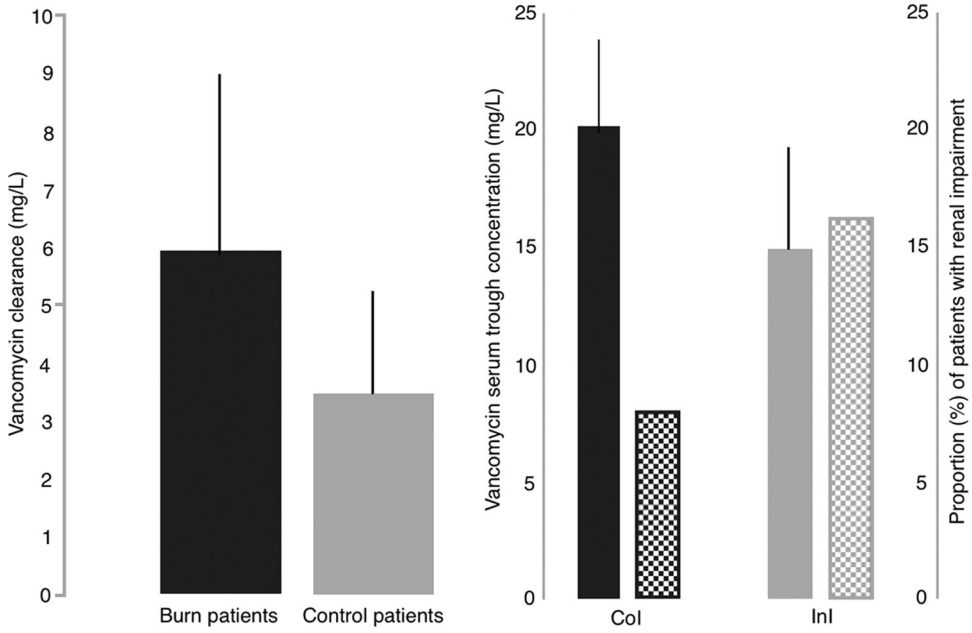

FIG 5 Burn patients have higher vancomycin clearance and lower serum trough levels than control patients, as found by Dolton et al. (64). In this context, vancomycin continuous infusion (CoI) may improve the achievement of the target serum trough levels (mean ± SD, solid bars) without increasing nephrotoxicity (gridded bars) (65), compared with patients receiving vancomycin intermittent infusion (InI) (evidence level IIC [83]).

ences in overall clinical outcome or toxicity, than were burn patients receiving intermittent infusion (65) (Fig. 5).

VANCOMYCIN IN CYSTIC FIBROSIS

Pharmacokinetics of antibiotics in patients with cystic fibrosis (CF) are altered in comparison to healthy people. The main differences reported are higher volume of distribution and total body clearance (66). However, specific information about the PK of vancomycin in this setting is very scarce.

Pleasants et al. (67) performed a PK study of vancomycin in CF patients. The values of several PK parameters (volume of distribution, total body clearance, and terminal elimination rates constant) were similar to those obtained in previous studies of healthy individuals. In contrast, Fung (68) described difficulties in achieving target trough levels with the current recommended dosages in three CF patients. In these cases, treatment administration was switched to continuous infusion, with successful clinical improvement, therapeutic steady-state level achievement, and absence of nephrotoxicity. The absence of further information does not allow specific recommendations for CF patients.

VANCOMYCIN TOXICITY

Vancomycin has been associated with several adverse events. Nephrotoxicity causes the most concern. Since it is related to serum vancomycin concentrations, the safety of current recommendations to target higher serum trough levels has been questioned. Some authors have proposed that AUC, not trough level, is the parameter best related to nephrotoxicity (24). However, to date, trough concentration is the most validated parameter to describe the drug exposure-toxicity relationship.

Vancomycin-induced nephrotoxicity is usually mild to moderate and reversible. It is defined in most publications as an increase of >0.5 mg/dl (or a >50% increase) in serum creatinine over baseline, in consecutively obtained daily serum creatinine values in the absence of an alternative justification (4). Even so, some authors have suggested that the new criteria of the Acute Kidney Injury Network, which include the reduction of urine output in the definition of renal function impairment, should be used (69). These criteria seem better to evaluate renal impairment in the clinical setting; thus, considering them, the real incidence of vancomycin-induced nephrotoxicity may differ from that previously reported.

Whether high vancomycin levels are a cause or an effect of renal function impairment has been a point of debate. A multicenter prospective clinical trial, including 288 adult patients (70), and a recent meta-analysis (71) have reaffirmed the high probability of nephrotoxicity with vancomycin trough levels of >15 mg/liter. This threshold is not uniform in all studies, and other authors have found that recommended dosages of vancomycin with target troughs of 15 to 20 mg/liter are not an independent risk factor for nephrotoxicity (72). Davies et al. (73) found that vancomycin was related to a rise in creatinine levels only with trough levels of >20 mg/liter. Additionally, Hanrahan et al. (37) showed that the risk of renal impairment among critically ill patients was related to higher serum levels, ranging from a RR of 1.07 for a trough of 15 mg/liter to a RR of 2.2 for a trough of >30 mg/liter. Other identified risk factors for renal function impairment during vancomycin therapy were duration of therapy, especially ≥7 days (37, 71, 74), previous renal insufficiency (75), and concomitant administration of nephrotoxic agents (37, 76, 77). Aminoglycosides gave specific cause for concern, and many studies described a higher rate of renal function impairment (up to 22%) when administered along with vancomycin (78, 79). With this combination, nephrotoxicity typically occurs after at least 5 days of therapy (80). Prevention of vancomycin-induced nephrotoxicity by using several antioxidant substances has shown beneficial effects in animal models but has not been confirmed by clinical trials yet (81).

How to manage vancomycin dosing in patients with renal failure has received little attention, and most clinicians are inclined to change the antibiotic. Nonetheless, the alternative drugs might not be tolerated and might not even available in some situations. In a small prospective study in patients receiving doses of vancomycin to achieve drug trough levels of 15 to 20 mg/liter and developing renal function impairment, Teng et al. (82) reported successful therapies and reversibility of renal impairment just by adjusting vancomycin dosages.

Vancomycin ototoxicity is controversial (4). The verifiable risk of vancomycin-induced hearing loss is low, and it does not seem to correlate to serum vancomycin concentration (76). Thus, monitoring serum vancomycin levels to prevent ototoxicity is not recommended (4).

CONCLUDING REMARKS

Vancomycin efficacy is related to its correct dosing according to optimal PK/PD parameters. An AUC/MIC ratio around 400 has been related to increased survival rates in patients with *S. aureus* bacteremia. Although trough vancomycin levels are not a perfect surrogate of AUC, achieving a trough concentration of 15 to 20 mg/liter would be enough to treat infections produced by *S. aureus* with a MIC_{Etest} of ≤1 mg/liter. Due to relevant interindividual variability, individualized doses are the best option, and Bayesian estimation procedures are the most accurate method to calculate them. Trials about special pharmacokinetic situations, such as obese patients or renal replacement therapy (RRT), are necessary. Vancomycin therapy for patients undergoing intermittent RRT should be individualized according to validated nomograms, and patient weight, dialyzer type, residual renal function, and interdialysis interval, helped by monitoring levels, should be considered. Continuous infusion of vancomycin may be helpful in those clinical situations, in which a high risk of toxicity and/or an increased variability in vancomycin levels are expected. Monitoring trough serum levels remains the best way to prevent nephrotoxicity. Clinicians must decide in each case, when nephrotoxicity occurs, whether to replace vancomycin with another active drug, knowing that continuing vancomycin under close surveillance is a valid option.

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